EXHIBIT C

1: Biochem Biophys Res Commun 2000 Nov 2;277(3):757-63

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Enhanced drug resistance in cells coexpressing ErbB2 with EGF receptor or ErbB3.

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Overexpression of ErbB2 has been found in approximately 25-30% of human breast cancers and has been shown to render the cancer cells more resistant to chemotherapy. However, it is not clear whether ErbB2 overexpression renders the cells more resistant to specific anti-cancer drugs or renders the cells more resistant to a broad range of anti-cancer drugs. It is not clear how the function of ErbB2 in drug resistance is related to expression and activation of the other ErbB receptors. In this communication, we showed that several breast cancer cell lines including BT20, BT474, MCF-7, MDA-MB-453, and SKBR-3 cells had a similar pattern of resistance to a broad range of anti-cancer drugs including 5-Fluorouracil, Cytoxan, Doxorubincin, Taxol, and Vinorelbin, suggesting a mechanism of multidrug resistance. High expression of P-glycoprotein and the ErbB receptors contribute to drug resistance of these breast cancer cells; however, overexpression of ErbB2 alone is not a major factor in determining drug resistance. To further determine the role of the ErbB receptors in drug resistance, we selected various NIH 3T3 cell lines that specifically expressed EGF receptor (EGFR), ErbB2, ErbB3, EGFR/ErbB2, EGFR/ErbB3, or ErbB2/ErbB3. A cytotoxicity assay showed that expression of ErbB2 alone did not significantly enhance drug resistance, whereas coexpression of either EGFR or ErbB3 with ErbB2 significantly enhanced drug resistance. Moreover, ErbB2 was highly phosphorylated in NIH 3T3 cells that coexpress ErbB2 with either EGFR or ErbB3, but not in NIH 3T3 cells that express ErbB2 alone. Together, our results suggest that coexpression of EGFR or ErbB3 with ErbB2 induces high phosphorylation of ErbB2 and renders the cells more resistant to various anti-cancer drugs. Copyright 2000 Academic Press.

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